Monocyte Mobilisation, Microbiota & Mental Illness

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Abstract

The gastrointestinal microbiome has emerged as a key player in regulating brain and behaviour. This has led to the strategy of targeting the gut microbiota to ameliorate disorders of the central nervous system. Understanding the underlying signalling pathways in which the microbiota impacts these disorders is crucial for the development of future therapeutics for improving CNS functionality. One of the major pathways through which the microbiota influences the brain is the immune system, where there is an increasing appreciation for the role of monocyte trafficking in regulating brain homeostasis. In this review, we will shed light on the role of monocyte trafficking as a relay of microbiota signals in conditions where the central nervous system is in disorder, such as stress, peripheral inflammation, ageing, traumatic brain injury, stroke, multiple sclerosis, Alzheimer's disease and Parkinson's disease. We also cover how the gastrointestinal microbiota is implicated in these mental illnesses. In addition, we aim to discuss how the monocyte system can be modulated by the gut microbiota to mitigate disorders of the central nervous system, which will lead to novel microbiota-targeted strategies.

1. Introduction

There is a growing recognition of the role of the gastrointestinal microbiota in regulating brain and behaviour, which has been coined the microbiota-gut-brain axis (Rhee et al. 2009, Collins et al. 2012, Cryan et al. 2012, Cryan et al. 2019). It is crucial to understand the signalling pathways underlying this axis in order to inform future therapeutics in improving CNS functionality in both health and disease. Some pathways have already been widely described, such as host immunity (Rea et al. 2016, Rieder et al. 2017), the vagus nerve (Bonaz et al. 2018, Fulling et al. 2019), metabolite production (Rooks et al. 2016), and enteroendocrine signalling (Plovier et al. 2017, van de Wouw et al. 2017, Lach et al. 2018). In tandem, there is a growing appreciation of the role of monocyte trafficking in regulating brain homeostasis and aiding the brain's response to insult or injury (Ramirez et al. 2017). In this review, we will shed more light on the role of monocyte trafficking as a relay of microbiota signals to the host CNS and its behavioural implications. In addition, we cover how this system can be modified using various microbiota-targeted strategies.

2. Monocytes: from Bone to Brain

Monocytes are mononuclear phagocytes that play crucial roles in tissue homeostasis and immunity, where they are especially important in inflammation and pathogen challenge. Monocytes, in particular those characterised by a high LY6C expression (i.e., LY6C^{hi}), originate in the bone marrow, after which they enter the peripheral circulation. These cells subsequently either differentiate into LY6C^{low} monocytes (Varol et al. 2007, Yona et al. 2013), or differentiate into dendritic cells or macrophages upon entering various tissues (**Figure 1**) (Ginhoux et al. 2014). Notably, specific dendritic cells and most tissue-resident macrophages (e.g., brain microglia) are maintained independently of peripheral monocyte contribution (Ajami et al. 2007, Liu et al. 2009, Varol et al. 2009, Hashimoto et al. 2013, Yona et al. 2013). For an overview of all circulating murine and human subsets, see **Table 1** (for further reading, see (Jakubzick et al. 2017, Guilliams et al. 2018)).

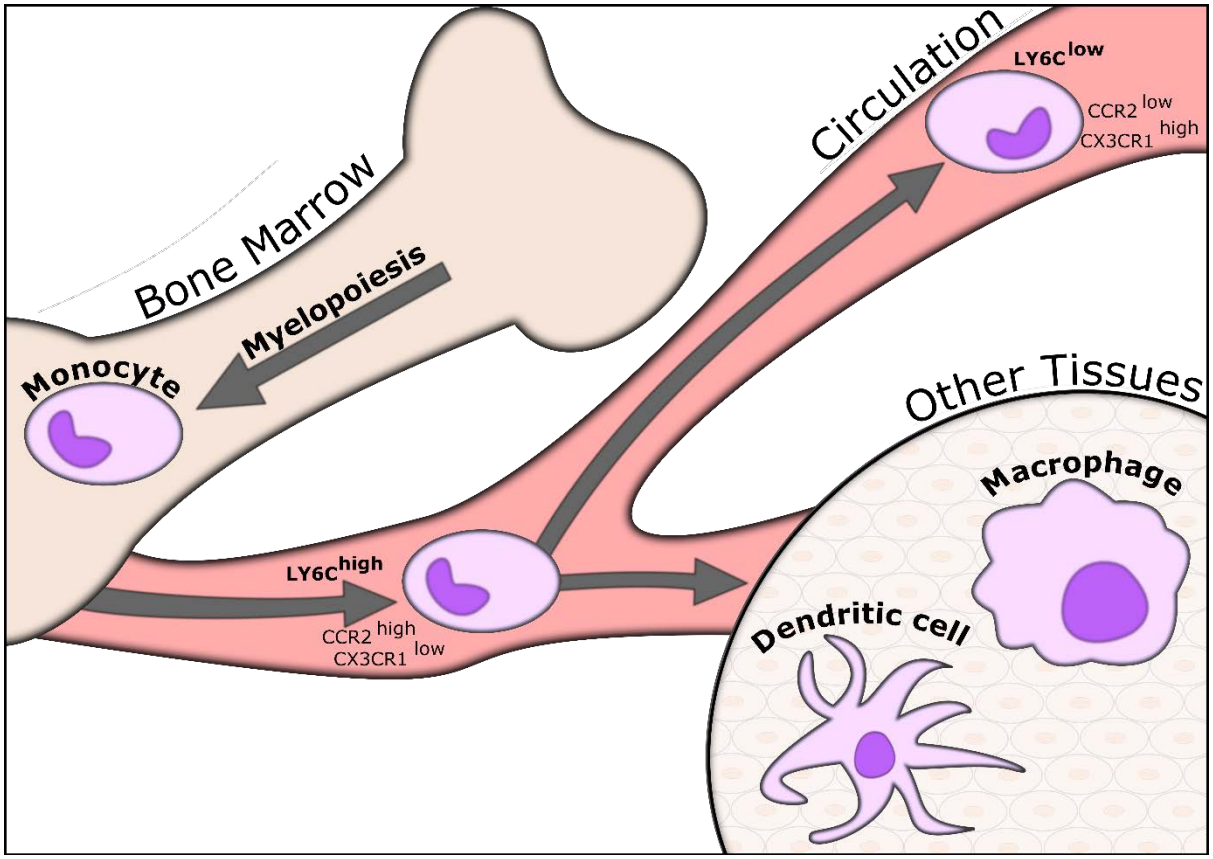

Figure 1. *The production and fate of monocytes. Monocytes are produced in the bone marrow through myelopoiesis. LY6C^{high} monocytes subsequently enter the peripheral circulation, after which they either differentiate into LY6C^{low} monocytes, or traffic into other tissues and differentiate in dendritic cells or macrophages. LY6C^{high} monocytes have a high expression of the CCR2 and low expression of the CX3CR1 receptor. LY6C^{low} monocytes have a low expression of the CCR2 and high expression of the CX3CR1 receptor.*

Table 1. Monocyte subsets and functions in mice and humans.

Species	Subsets	Surface markers	Chemokine receptors	Function	References
Mouse	LY6C^{hi}	CD11b^{+}, LY6C^{hi}	CCR2^{hi}, CX3CR1^{Low}	Phagocytosis & Pro-inflammatory	(Palframan et al. 2001, Geissmann et al. 2003, Auffray et al. 2007, Ziegler-Heitbrock et al. 2010)
	LY6C^{mid}	CD11b^{+}, LY6C^{mid}	CCR2^{hi}, CX3CR1^{Low}	Pro-inflammatory	
	LY6C^{low}	CD11b^{+}, LY6C^{low}	CCR2^{low}, CX3CR1^{hi}	Patrolling; tissue repair	
Human	Classical	CD14^{++}, CD16^{-}	CCR2^{hi}, CX3CR1^{Low}	Phagocytosis	(Passlick et al. 1989, Ziegler-Heitbrock et al. 2010, Ziegler-Heitbrock et al. 2013, Patel et al. 2017)
	Intermediate	CD14^{++}, CD16^{+}	CCR2^{mid}, CX3CR1^{hi}, CCR5^{+}	Pro-inflammatory	
	Non-classical	CD14^{+}, CD16^{++}	CCR2^{low}, CX3CR1^{hi},	Patrolling	

Infiltration of monocytes into the CNS occurs at a steady-state under non-pathological conditions (Korin et al. 2017, Mrdjen et al. 2018), which has been implicated in brain plasticity (Mohle et al. 2016). Enhanced monocyte trafficking often occurs during various pathological conditions where monocytes can facilitate tissue injury, repair or protection (Ransohoff et al. 2010, Prinz et al. 2011, Ransohoff 2011, Karlmark et al. 2012). Infiltrating monocytes/macrophages exhibit a molecularly and functionally distinct signature compared to the most prominent myeloid cells present in the brain - the microglia (Ginhoux et al. 2010, Hickman et al. 2013, Butovsky et al. 2014, Cronk et al. 2018, Lund et al. 2018). Enhanced cell trafficking can occur through the choroid plexus-cerebrospinal fluid route in many conditions such as stroke (Ge et al. 2017), and traumatic brain injury (TBI) (Szmydynger-Chodobska et al. 2012). In addition, many conditions associated with enhanced cell trafficking into the CNS are often paired with an increased blood-brain barrier permeability, likely allowing monocyte to more easily infiltrate into brain tissue (Takeshita et al. 2012). More recently, it has been shown that myeloid cells can migrate to the brain through vascular channels from the bone marrow in conditions of stroke and aseptic meningitis (Herisson et al. 2018). Under conditions of neuroinflammation, activated microglia release the chemokine C-C motif chemokine ligand 2 (CCL2) and the chemokine (C-X3-C motif) ligand 1 (CX3CL1) (Prinz et al. 2010). The receptors for these ligands, CCR2 and CX3CR1, are expressed on monocytes and subsequently facilitate monocyte trafficking into the brain (Prinz et al. 2010). Whether monocytes play a causal role in the symptomology in specific conditions is often investigated using CCR2-KO or CX3CR1-KO mice, in which monocyte trafficking (into the CNS) is almost ablated (Tsou et al. 2007, Prinz et al. 2010). It is also interesting to note that the CXCR7 receptor has recently been implicated in classical monocyte trafficking into the brain in relation to HIV-associated neurocognitive disorders in humans (Veenstra et al. 2017). Moreover, CCR7 can facilitate TLR4-induced trans-migration of monocytes across the blood-brain barrier *in vitro* (Paradis et al. 2016).

3. Gut microbial shaping of the monocyte system and monocyte function

3.1 The Microbiota in Monocyte Trafficking

Proof-of-principle studies using mice devoid of any microbiota (i.e., germ-free – GF) have revealed that the microbiota is essential for hematopoiesis, as these mice show decreased levels of monocytes in the bone marrow, spleen, and circulation (Balmer et al. 2014, Khosravi et al. 2014). These deficits are ameliorated upon recolonisation of the microbiota or by the administration of microbial-associated molecular patterns (MAMPs) (Khosravi et al. 2014). Similar to GF mice, depletion of the gastrointestinal microbiota by antibiotic administration decreases systemic and brain LY6C^{hi} monocyte levels (Balmer et al. 2014, Khosravi et al. 2014, Möhle et al. 2016), which is restored upon supplementation with the multispecies probiotic VSL#3, which contains eight bacterial strains: *Bifidobacterium breve*, *B. infantis*, *B. longum*, *Lactobacillus acidophilus*, *L. delbrueckii*, *L. paracasei*, *L. plantarum* and *Streptococcus thermophilus* (Mohle et al. 2016). Interestingly, this study also showed that microbiota-regulated monocyte trafficking is essential for healthy adult hippocampal neurogenesis and memory retention (Möhle et al. 2016). Off note, GF mice also show deficits in microglia maturation and function, which is paired with an increase in macrophage colony-stimulating factor 1 receptor expression (CSF1R) on microglia, a key factor in neuron-microglia interactions, indicating a possible role for the gut microbiota in regulating neuron-microglia cross-talk (Erny et al. 2015, Wohleb 2016). Administration of the endotoxin lipopolysaccharide (LPS), a microbiota-derived metabolite, increases monocyte trafficking into the CNS and sickness behaviour (Harden et al. 2015, Rosadini et al. 2017), indicating a role for the microbiota in monocyte-associated neuroinflammation and subsequent behavioural impairment. It is also interesting to note that monocytes can contribute to pathogen dissemination into the brain by carrying microbiota-derived bacterial strains resulting in brain infection (Drevets et al. 2004, Santiago-Tirado et al. 2017).

3.2 Microbial Metabolites and Epigenetic Programming

There is a growing emphasis on the role of microbial metabolites as epigenetic regulators (Stilling et al. 2016, Woo et al. 2017). This is important in regard to monocyte trafficking as prior to their infiltration into tissue and subsequent differentiation into macrophages, monocytes can undergo a trained innate immunity via epigenetic reprogramming, which subsequently determines the function of the cells they differentiate into (Bordon 2014, Guilliams et al. 2018). Innate memory training of monocytes has been implicated in the susceptibility to secondary infections and the functional fate of macrophages (Quintin et al. 2012, Bordon 2014, Cheng et al. 2014), and has even been linked to the pathogenesis of neuroimmune psychiatric disorders (Salam et al. 2018). Various microbiota-derived metabolites have already been shown to facilitate trained innate immunity, such as β-glucan, LPS, and butyrate (Saeed et al. 2014, Schulthess et al. 2019). Such data indicates the possibility for the development of microbiota-targeted strategies to reprogram monocytes before their infiltration into the brain to influence the brain and behaviour in healthy and pathogenic conditions (**Figure 2**).

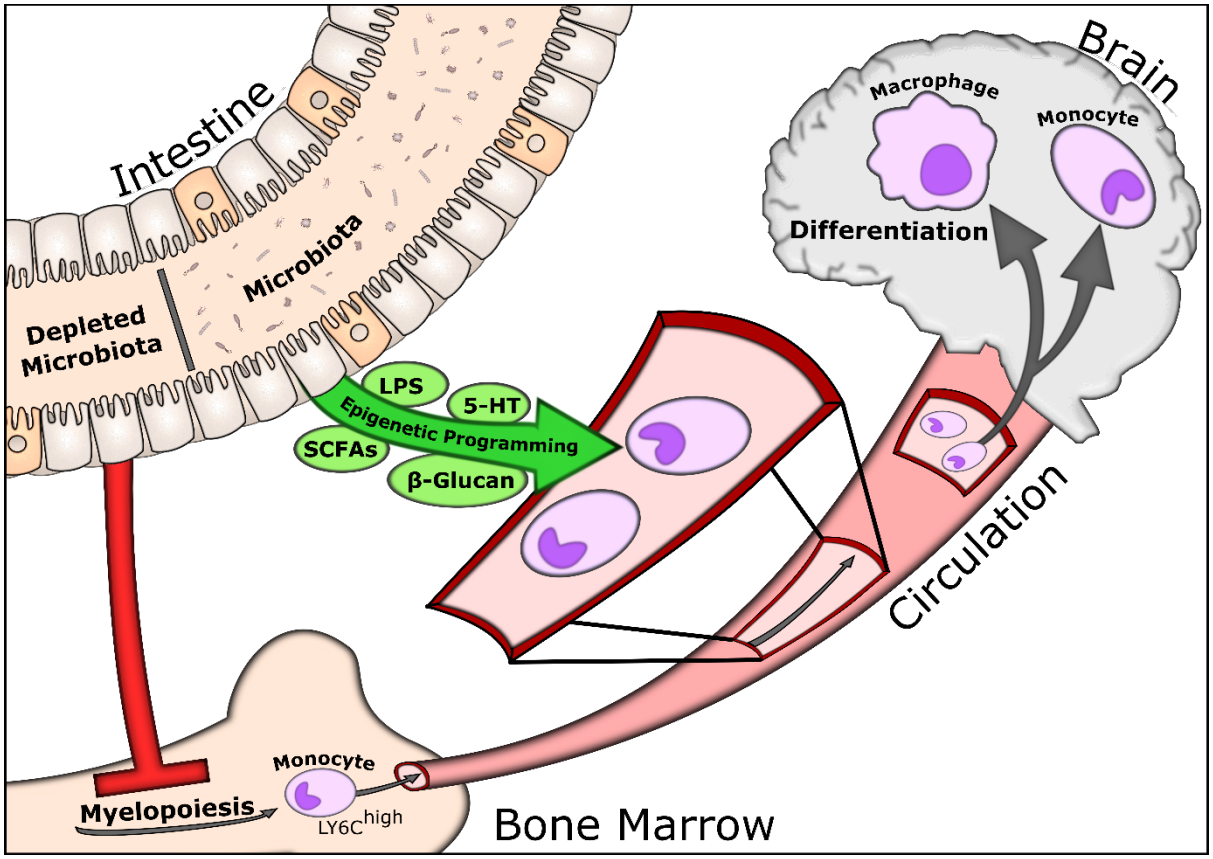

***Figure 2**: Pathways in which the microbiota can influence monocyte trafficking to the brain and subsequent signalling. A depleted gastrointestinal microbiota results in a decreased myelopoiesis and monocyte levels, resulting in reduced monocyte trafficking to the brain. Alternatively, gut microbiota-derived metabolites, such as lipopolysaccharide (LPS), serotonin (5-HT), SCFAs (short-chain fatty acids), and β-glucans, can influence monocyte properties and the macrophages they subsequently differentiate into.*

Perhaps one of the most investigated microbial-derived metabolites is the endotoxin LPS, which is present on the outer membrane of Gram-negative bacteria. LPS activates the toll-like receptor 4 (TLR4) and its co-receptors, CD14 and myeloid differentiation protein 2, resulting in the secretion of various inflammatory cytokines (Rossol et al. 2011, Cavaillon 2018). Incubation of human monocytes with LPS *ex vivo* reprograms monocytes to differentiate into macrophages (i.e., trained immunity) secreting less pro-inflammatory cytokines, such as TNF-α and IL-6 (Saeed et al. 2014).

β-glucans are polysaccharides naturally occurring in cell walls of plants, bacteria, and fungi. The direct effects of β-glucans on immune cells are most likely mediated by cell-surface receptors such as dectin-1 and TLRs, as β-glucans cannot penetrate the cell membrane (Kim et al. 2011). Similar to LPS, β-glucans have also been shown to elicit trained innate immunity (Cheng et al. 2014, Saeed et al. 2014). Specifically, incubation of human monocytes with β-glucan *ex vivo* can reprogram monocytes to differentiate into macrophages secreting more pro-inflammatory mediators, such as TNF-α and IL-6, upon subsequent stimulation with a TLR2 receptor ligand (Cheng et al. 2014, Saeed et al. 2014). It is important to note however, that the immunomodulatory effect of β-glucans is primarily dependent on the source they have been extracted from (for review see: (Sima et al. 2018)).

Another class of gut microbial-derived metabolites known to affect monocyte function are short-chain fatty acids (SCFAs) (for a comprehensive review on SCFAs and host physiology, see: (Koh et al. 2016, Stilling et al. 2016)). The primary source of SCFAs is the microbial fermentation of host-indigestible dietary fibres in the cecum and colon (Macfarlane et al. 2003). The three principle SCFAs are acetate, propionate and butyrate, of which only acetate reaches the peripheral circulation in high concentrations (100–200 µmol/L, 1- to 15- µmol/L for propionate and butyrate) (Cummings et al. 1987, Peters et al. 1992, Bloemen et al. 2009). Data indicate an anti-inflammatory effect of SCFA on monocytes, as well as other immune cell populations (Li et al. 2018). All three principle SCFAs can activate the free fatty acid receptor 2 and 3 (FFAR2 and FFAR3 respectively), which are expressed on murine and human monocytes and suppress LPS-induced cytokine secretion (Ang et al. 2016).

Similarly, butyrate inhibits *Staphylococcus aureus*-induced IL-12p40, IL-12p70, and TNF-α secretion, while enhancing IL-10 secretion in human monocytes (Saemann et al. 2000). In addition, human monocytes treated with butyrate have a decreased expression of the innate response receptors CD14 and CD16, which was mediated through the downregulation of the transcription factor PU.1 (Lasitschka et al. 2017), which has been implicated in monocyte/macrophage differentiation (Shen et al. 2016). Indeed, it has recently been shown that human monocytes incubated with butyrate differentiate into macrophages with potent antimicrobial function (Schulthess et al. 2019). In addition, a 4-week oral supplementation of butyrate to individuals with metabolic syndrome influenced subsequent *ex vivo* trained immunity by oxidised low-density lipoprotein, resulting in decreased LPS-induced IL-6 secretion and Pam3CSK4-induced TNF-α secretion, as well as a decreased Pam3CSK4-induced IL-10 production when monocytes were trained with β-glucan (Cleophas et al. 2019).

One of the most studied neurotransmitter systems regulated by the gut microbiota and its metabolites is serotonin (5-HT) (Clarke et al. 2013, Yano et al. 2015). A variety of 5-HT receptors are expressed on monocytes such as the 5-HT1A, 5-HT1E, 5-HT2A, 5-HT3A, 5-HT4 and 5-HT7 receptor (Herr et al. 2017). In addition, monocytes express the serotonin transporter and the key enzymes involved in serotonin synthesis (tryptophan hydroxylase - TPH) and for serotonin degradation (monoamine oxidase- MAO) (Herr et al. 2017). Serotonergic signalling in monocytes increases the LPS-induced secretion of the inflammatory cytokines IL-1β, IL-6, IL-12p40, and IL-8, yet decreases TNF-α (Arzt et al. 1991, Cloez-Tayarani et al. 2003, Durk et al. 2005), highlighting a complex modulatory effect of 5-HT on monocytes. Conversely, 5-HT is also able to influence monocyte to macrophage differentiation, resulting in a decreased LPS-induced inflammatory cytokine release (de las Casas-Engel et al. 2013), potentially showing a role for 5-HT in trained innate immunity.

4. Gut microbiota-targeted therapeutics

There are at many ways by which the gut microbiota can be targeted (long-Smith et al. 2019). For instance, by administrating live bacterial strains that confer health benefits (i.e. probiotics) (Hill et al.

2014, Derrien et al. 2015). Alternatively, administration of host-indigestible dietary fibers, which undergo bacterial fermentation, subsequently stimulates the growth of certain types of bacteria (i.e. prebiotics) (Bindels et al. 2015, Gibson et al. 2017, Stephen et al. 2017). There is also an increased emphasis on synbiotic (i.e. combining both pre- and probiotics) and post-biotics (i.e. microbial-derived metabolites) approaches (Markowiak et al. 2017, Aguilar-Toalá et al. 2018), as well as fermented foods (Kim et al. 2016). If these various microbiota-targeted therapeutics confer mental health benefits, then they are also considered psychobiotics (Dinan et al. 2013, Sarkar et al. 2016). Transplanting the faecal microbiota is also becoming more widely used (Ridaura et al. 2013, Smits et al. 2013, Kelly et al. 2016, Bakker et al. 2017, Kang et al. 2019). Finally, there are also various strategies for depleting specific gut microbes, such as antibiotics (Ianiro et al. 2016, Langdon et al. 2016), and bacteriophages (Dalmasso et al. 2014).

It is also important to note that nutritional interventions can modulate the gut microbiota (Sandhu et al. 2017). For instance, omega-3 fatty acids have been shown to modulate the murine (Pusceddu et al. 2015, Robertson et al. 2017, Provensi et al. 2019), and human gut microbiota (Costantini et al. 2017). In addition, various polyphenols can modulate the composition of the gut microbiota in both rodents (Chen et al. 2016, Sung et al. 2017, Zhou et al. 2018, Campbell et al. 2019), and humans (Most et al. 2017). Similarly, other micronutrients such as vitamin D can modulate the host microbiota (Luthold et al. 2017).

5. Conditions Linked to Increased Monocyte Trafficking

5.1 Acute and Chronic Stress

Stress can be defined as a complex condition wherein the homeostasis of an organism is disturbed (McEwen et al. 2015). This results in an internal response of the organism governed by the hypothalamic-pituitary-adrenal axis (HPA-axis), where the hypothalamus secretes corticotropin-releasing hormone (CRH), stimulating the pituitary gland to secrete adrenocorticotropic hormone (ACTH), resulting in a secretion of cortisol (corticosterone for rodents) by the adrenal glands (Uschold-

Schmidt et al. 2012, Uschold-Schmidt et al. 2013). Activation of the HPA-axis results in altered levels of glucocorticoids and mineralocorticoids aimed to change the behaviour of the organism. This system becomes hyperactivated upon repeated acute stressors (i.e. chronic stress) resulting in decreased evening corticosterone, a hypersensitive HPA-axis and delayed HPA-axis recovery (Bhatnagar et al. 2006, Finger et al. 2011, Wagner et al. 2011, Uschold-Schmidt et al. 2012, Fuchsl et al. 2013, Iniguez et al. 2014, Langgartner et al. 2016, Peterlik et al. 2017). The crucial role of the HPA-axis within the development of stress-related disorders is highlighted by mouse studies demonstrating an amelioration of chronic stress-induced impairments by the blockade of HPA-axis-related mechanisms, such as corticotropin-releasing factor-2 receptor blockade and adrenalectomy (Cooper et al. 2010, Niraula et al. 2018).

Acute stress and HPA-axis activation are paired with an activation of the immune system as measured by a systemic release of cytokines, and by an increased secretion of cytokines upon immune cell stimulation with LPS and phytohaemagglutinin *ex vivo* (Marsland et al. 2017). However, the elevation of glucocorticoids upon HPA-axis activation is mostly implicated in suppressing the further inflammatory response to an acute stressor (Sapolsky et al. 2000). Glucocorticoids are therefore well-known for their anti-inflammatory effects as determined by their ability to inhibit the expression and action of most cytokines (Brattsand et al. 1996, Coutinho et al. 2011). It is not surprising that they have been the cornerstone for treating inflammatory disease for over 60 years (Hench et al. 1950). However, it is important to note that both acute stress and glucocorticoid administration prior to an LPS challenge potentiate inflammation (Johnson et al. 2002, Frank et al. 2010, Sorrells et al. 2013, Kelly et al. 2018), indicating that glucocorticoids can facilitate both the priming and resolving of inflammation (Sorrells et al. 2010).

Rodent studies exploring how stress influences the immune system have revealed decreased levels of circulating monocyte levels in response to acute stress (Dhabhar et al. 1994), indicating an enhanced monocyte trafficking (Dhabhar et al. 2012). Similarly, cold water-induced stress decreases circulating

monocyte levels in healthy male volunteers (Brazaitis et al. 2014). Stress-induced monocyte trafficking is largely mediated by glucocorticoids, as stress-induced monocyte trafficking is absent in adrenalectomised animals in the active-phase, and is only partially present in the inactive-phase of the day (Dhabhar et al. 1995). In addition, corticosterone administration induces monocyte trafficking in rodents (Dhabhar et al. 2012), while glucocorticoids decrease peripheral monocyte levels in healthy human volunteers (Fauci et al. 1974, Steer et al. 1998, Olnes et al. 2016, Yeager et al. 2016). It is, to our knowledge, still unclear whether monocytes traffic into the brain response to an acute stressor. Even though it is interesting to note that acute stress does induce leukocyte trafficking into the skin (Dhabhar et al. 1996). No differences were found in CNS monocyte levels 14-hours post-stress (Wohleb et al. 2013), even though these acute stress-induced effects might have dissipated at this time point, considering that peripheral monocyte levels are back to baseline 3 hours after an acute stressor (Dhabhar et al. 1995). Notably, there is an increased gene expression of adhesion factors (i.e., ICAM1, VCAM1, E-selectin) and chemokines (i.e., CXCL1 and CXCL2) 14-hours post-stress (Sawicki et al. 2015), which might indicate an enhanced sensitivity for monocytes to traffic and adhere to the CNS in repeated episodes of acute stress.

In line with the fact that acute stress results in activation of the immune system (Marsland et al. 2017), repeated stressors result in sustained low-grade inflammation (Hansel et al. 2010, Rohleder 2014, Langgartner et al. 2018, Niraula et al. 2018). One of the key aspects of this low-grade inflammation is monocytosis as indicated by an increased production of monocytes in the bone marrow (Heidt et al. 2014), and increased levels of circulating, splenic and brain monocytes (Engler et al. 2004, Engler et al. 2005, Engler et al. 2008, Hanke et al. 2012, Wohleb et al. 2014, Sawicki et al. 2015, McKim et al. 2016, Lafuse et al. 2017, Lisboa et al. 2018, McKim et al. 2018, Nie et al. 2018, Gururajan et al. 2019, Yin et al. 2019). Similarly, individuals with a low socioeconomic status, akin to chronic social stress, have increased levels of circulating monocytes (Powell et al. 2013). Monocyte trafficking into the brain is further supported by an increase in blood-brain-barrier permeability in response to chronic stress (Rodriguez-Arias et al. 2015, Lehmann et al. 2018).

The mechanistic role for the monocyte system in the aetiology of chronic stress disorders is indicated by rodent studies utilising knock-out models of CCR2-CCL2 signalling, which is essential for monocyte infiltration into the CNS (Prinz et al. 2010). These studies have revealed that monocyte trafficking mediates chronic stress-induced anxiety-like behaviour (Wohleb et al. 2013). Similarly, chemical dampening of Ly6C^{hi} monocytes in chronically stressed mice ameliorates anhedonia, anxiety-like behaviour and markers of neuroinflammation in the hippocampus, hypothalamus and cortex (Zheng et al. 2016). It is important to note, however, that one study reported the absence of CCR2+ monocyte trafficking into the brain in response to social defeat stress, and that CCR2-KO mice show no alterations in stress-induced microglia activation and depressive-like behaviour (Lehmann et al. 2016).

Glucocorticoids also affect the function of monocytes themselves, which is not surprising considering the expression of glucocorticoid receptors on monocytes (Miller et al. 1998). Similar to the decrease in circulating monocyte levels observed in response to an acute stressor (Dhabhar et al. 2012), murine monocyte treated with glucocorticoids *ex vivo* have an increased migratory and chemotaxic activity (Ehrchen et al. 2007). Specifically, glucocorticoid treated human monocytes upregulate the expression of the trafficking receptor CCR2 and have enhanced CCL2-induced chemotaxis (Penton-Rol et al. 1999, Okutsu et al. 2008, Yeager et al. 2016). Functionally, glucocorticoids suppress cytokine secretion upon an immune stimulus, which has been linked to the transcription factors NF-κB and AP-1 (Coutinho et al. 2011). This is supported by the fact that murine monocytes treated with glucocorticoids have increased phagocytic activity, decreased oxidative burst and apoptosis, and modify T cell responses in an anti-inflammatory manner (Ehrchen et al. 2007, Varga et al. 2014). In fact, glucocorticoids induce the differentiation of monocytes into an activated, anti-inflammatory subset (Varga et al. 2008, Tsianakas et al. 2012). Interestingly, chronic stress is associated with a decreased responsiveness of immune cells to glucocorticoids (Engler et al. 2004, Bailey et al. 2007, Engler et al. 2008, Niraula et al. 2018), which has been coined glucocorticoid resistance (Miller et al. 2002). Importantly, the development of psychosocial stress-induced glucocorticoid resistance in mice is dependent on physical injury (Foertsch et al. 2017).

5.1.1 The Microbiota in Acute and Chronic Stress

Proof-of-principle studies using mice devoid of any microbiota (i.e. germ-free, GF) have demonstrated a role for the microbiota in stress responsiveness (Sudo et al. 2004, Vodicka et al. 2018), and stress-related receptor pathway genes in the hippocampus (Luo et al. 2018). This postulates the rationale for modulating acute stress-responses using microbiota-targeted strategies. Indeed, bacterial strains such as *L. rhamnosus* and *B. bifidum* reduce HPA-axis reactivity in rodents (Bravo et al. 2011, Fukui et al. 2018), and a *B. longum* strain in healthy volunteers (Allen et al. 2016). Similarly, the prebiotic sugars fructooligosaccharides (FOS) and galactooligosaccharides (GOS) decreases stress-responsiveness in rodents (Burokas et al. 2017), and a supplement containing FOS and B-GOS decreases cortisol levels in humans (Schmidt et al. 2015). The combination of *L. casei* and inulin (i.e. synbiotics), decreases stress-responsiveness in rats (Barrera-Bugueno et al. 2017). And not surprisingly, administration of the microbial-derived metabolites SCFAs, which are mostly derived from the gut microbial fermentation of dietary fibres, ameliorates stress-responsiveness in mice that had previously undergone psychosocial stress (van de Wouw et al. 2018).

In conditions of chronic stress, alterations in the composition and functional capacity of the gut microbiota have been detected in rodent models (Bailey et al. 2011, Galley et al. 2014, Bharwani et al. 2017, Burokas et al. 2017, Galley et al. 2017, Marin et al. 2017, Szyszkowicz et al. 2017, Dunphy-Doherty et al. 2018). Considering that microbiota-targeted strategies can reduce the response to an acute stressor, it is not surprising that these strategies are also able to reduce chronic stress-induced deficits in behaviour. For instance, supplementation of various bacterial strains from the class *Lactobacillus* results in beneficial effects on chronic stress-induced cognitive impairments, anxiety- and depressive-like behaviour in rodents (Liang et al. 2015, Bharwani et al. 2017, Marin et al. 2017, Dhaliwal et al. 2018, Li et al. 2018). Similarly, the bacterial strains L*. casei Shirota YIT 9029* and *L. plantarum 299v* reduce cortisol levels in students undergoing exam stress (Andersson et al. 2016, Takada et al. 2016). Prebiotic supplementation in mice undergoing psychosocial stress prevents deficits in stress-responsiveness, anxiety- and depressive-like behaviour in mice (Tarr et al. 2015,

Burokas et al. 2017). Moreover, administration of the microbial-derived metabolites SCFAs ameliorates stress-induced deficits in reward-seeking behaviour and stress-responsiveness (van de Wouw et al. 2018).

Overall, these data show great promise for gut microbiota-targeted nutritional interventions for alleviating stress-related conditions. Overall, the fact that acute stress and glucocorticoids can influence monocyte functionality makes monocytes an interesting target in alleviating stress-related disorders. Nonetheless, more research is warranted on monocyte receptors and (associated) signalling pathways to develop further targeted nutritional interventions for stress-related disorders.

5.2 Peripheral Inflammation, Encephalitis and Sickness Behaviour

Sickness behaviour is a crucial part of the body's mechanisms in the battling of, and recovering from infectious disease (Harden et al. 2015). The core symptoms associated with sickness behaviour are fatigue, social withdrawal, malaise, hyperalgesia, disturbed sleep and cognitive dysfunction, and a loss of appetite and interest in usual daily activities (Harden et al. 2015). These symptoms are often the result of increased pro-inflammatory cytokine signalling in the CNS originating from the periphery (Dantzer et al. 2008). Even though sickness behaviour during infectious disease expedites recovery, enduring immune activation in the brain can exacerbate sickness behaviour and induce the development of depression symptomatology in vulnerable individuals (Dantzer et al. 2008). One aspect of sickness behaviour-associated inflammatory signalling is monocytosis and increased CCR2+ monocyte trafficking into the CNS (Kerfoot et al. 2006, Getts et al. 2008, D'Mello et al. 2009, D'Mello et al. 2013, D'Mello et al. 2015, White et al. 2016, D'Mello et al. 2017, Andonegui et al. 2018, Canivet et al. 2019). The role of monocyte trafficking in sickness behaviour is demonstrated by the fact that CCR2-KO mice do not show any cognitive impairments induced by *Streptococcus pneumoniae* infection (Andonegui et al. 2018). Similarly, blockade of hepatic inflammation-induced monocyte trafficking into the brain using anti-P selectin and anti-α4 integrin attenuates sickness behaviour (D'Mello et al. 2009). This study also showed the necessity of TNF-α signalling in the recruitment of monocytes into the CNS

in mice with hepatic inflammation (D'Mello et al. 2009). It is therefore also interesting to note that peripheral and central TNF-α signalling induces sickness behaviour (Palin et al. 2007, Klaus et al. 2016). Moreover, understanding how monocyte trafficking contributes to such pathways may also have implications for understanding and managing aspects of human fatigue (Dantzer et al. 2014).

It is also interesting to note that, similar to peripheral inflammation, virus infection-induced encephalitis promotes CX3CR1+ monocytes trafficking into the brain and TNF-α signalling, which has been implicated in synaptic and learning deficits (Garre et al. 2017). A causal role of monocytosis and monocyte trafficking in the development of neuroinflammation is revealed by the use of CCR2-KO and CX3CR1-KO mice, which show a prolonged survival and prevention of neuroinflammation and neuronal death in response to viral encephalitis, even though seizure development remains unaffected (Kaufer et al. 2018).

5.2.1 The Microbiota in Peripheral Inflammation and Sickness Behaviour

Inflammation-induced anxiety-like behaviour caused by the administration of LPS administration is ameliorated by supplementation of the prebiotic GOS mixed with lactose, glucose and galactose in mice (Savignac et al. 2016). Similarly, bile duct ligation-induced sickness behaviour is ameliorated by administration of the probiotic VSL#3, and reduces monocyte infiltration into the brain and microglia activation (D'Mello et al. 2015). These data indicate a promising role for microbiota-targeted strategies in ameliorating sickness behaviour, potentially through reducing monocyte trafficking.

5.3 Ageing

The immune system undergoes a dynamic change during the process of ageing, which is often characterised by a chronic low-grade inflammation, also termed inflammageing (Franceschi et al. 2000, Oishi et al. 2016). This is associated with a decreased response to various immune stimuli, defined as immunosenescence (van Duin et al. 2007, Shaw et al. 2013, Frasca et al. 2016). In addition, microbial metabolites such as LPS are systemically elevated, potentially due to an increase in intestinal permeability, which may contribute to inflammageing (Kim et al. 2016, Scott et al. 2017). One key

aspect of ageing-associated inflammation is monocytosis and increased myeloid cell levels in the brain (Martinez et al. 2015, Puchta et al. 2016, Martin et al. 2017, Boehme et al. 2019). Furthermore, these monocytes are primed to produce more cytokines in response to LPS (Hearps et al. 2012, Puchta et al. 2016). One critical factor driving age-related monocytosis and dysfunction is the inflammatory cytokine TNF-α (Puchta et al. 2016), which is also able to polarise macrophages into a proinflammatory state (Oishi et al. 2016). Increased circulating and intracellular levels of TNF-α have been reported in monocytes of ageing individuals (Bruunsgaard et al. 1999, Hearps et al. 2012). It is also interesting to note that age-related memory decline is correlated with longitudinal increases in CCL2 levels (Bettcher et al. 2019), further indicating that the monocyte system adapts a more pro-inflammatory phenotype in response to ageing. It is also important to note that ageing is associated with a deterioration of other systems associated with monocyte trafficking, such as the HPA-axis (Vitlic et al. 2014), as well as an increased vulnerability to conditions associated with monocyte trafficking, such as TBI and stroke (Crapser et al. 2016, Sun et al. 2019).

5.3.1 The Microbiota in Ageing

Shifts in the composition of the gut microbiota with age have been detected in rodent models (Fransen et al. 2017, Scott et al. 2017, Thevaranjan et al. 2017, Spychala et al. 2018, van der Lugt et al. 2018, Boehme et al. 2019), and humans (Biagi et al. 2010, Claesson et al. 2012). Targeting the microbiota using a prebiotic-enriched diet ameliorates both monocyte influx and subsequent microglia activation in middle-aged mice (Boehme et al. 2019). This is in line with another study demonstrating that a high fibre diet containing inulin reduces the expression of inflammatory markers in microglia of aged mice (Matt et al. 2018). Similarly, supplementation of the probiotic *L. plantarum KY1032* and *L. curvatus HY7601* ameliorates memory impairments in aged rats (Jeong et al. 2015), while *L. helveticus IDCC3801* improves cognition in aged adults (Chung et al. 2014). Notably, the bacterial strain *L. reuteri DSM 17938* does not affect measures of depression, anxiety and perceived stress in aged adults (Östlund-Lagerström et al. 2016), potentially indicating that the positive effects of probiotics on age-associated deficits might be bacterial strain dependent.

5.4 Traumatic Brain Injury

The attraction of Ly6C^{hi}-monocytes to the site of the lesion is an early response phenomenon in TBI, resulting in neuroinflammation (Hsieh et al. 2013, Loane et al. 2016, Makinde et al. 2017). The importance of monocyte trafficking within TBI symptomatology is indicated by studies using CCR2-KO mice, as these mice show a decreased lesion volume, decreased pro-inflammatory response and improved cognition following TBI (Hsieh et al. 2014, Israelsson et al. 2014, Gyoneva et al. 2015, Chou et al. 2018). Similarly, CCR2 antagonism results in the downregulation of the pro-inflammatory response and long-term cognitive dysfunction in response to TBI (Morganti et al. 2015). Whereas the cognate ligand of the CCR2 receptor, the chemokine CCL2, is upregulated in the first hours following TBI in both humans (Semple et al. 2010) and rodents (Israelsson et al. 2008, Rhodes et al. 2009). The importance of monocyte trafficking is further indicated by the fact that monocyte depletion attenuates TBI-induced ventricle enlargement and improves neural connectivity, even though lesion size remains unaffected (Makinde et al. 2018). It is interesting to note, however, that CX3CR1-KO mice show reduced sensorimotor deficits and cellular damage four days post-TBI, which was subsequently worsened five weeks post-TBI (Zanier et al. 2016). Such data might indicate that CX3CR1+ monocyte trafficking is involved in long-term tissue repair and the resolving of inflammation in TBI. Conversely, CCR2-KO mice show decreased TBI-induced long-term cognitive impairments (Hsieh et al. 2014, Morganti et al. 2015), indicating that long-term impairments might be modulated by monocytes in a subset-specific manner.

5.4.1 The Microbiota in Traumatic Brain Injury

The composition of the gastrointestinal microbiota changes in response to TBI in mice (Treangen et al. 2018). Targeting the microbiota by supplementing *Clostridium butyricum* to mice that underwent TBI results in an amelioration in neurological severity score, brain oedema and neurodegeneration (Li et al. 2018). Similar findings have been reported for *L. acidophilus* showing an ameliorated neurological severity score, neurodegeneration and lesion volume (Ma et al. 2019). Furthermore, *B. longum*, *L. bulgaricus*, and *Streptococcus thermophilus* supplementation shortens the stay in the intensive care

unit of TBI patients (Tan et al. 2011). Which has also been reported for TBI patients receiving a formulation containing (glutamine and) fermented milk with *L. johnsonii* (Falcão de Arruda et al. 2004). Overall, findings suggest some promise in reducing TBI-symptomatology using microbiota-targeted strategies, but more evidence is warranted (Brenner et al. 2017).

5.5 Stroke

Stroke is characterized by a disruption of the blood supply to the CNS leading to focal ischemia, apoptosis, neuroinflammation, and functional decline, and is also associated with increased monocyte trafficking into the CNS (Wattananit et al. 2016, Ge et al. 2017, Weise et al. 2017, Garcia-Bonilla et al. 2018). Trafficking of monocytes into the CNS following a stroke can occur through the choroid plexus-cerebrospinal fluid route (Ge et al. 2017), as well as through the blood-brain barrier, which is more permeable in response to stroke (Moskowitz et al. 2010). These infiltrated monocytes subsequent contribute to the recovery from stroke (Wattananit et al. 2016). In addition, LPS-induced immune system priming enhances monocyte trafficking into the brain and suppresses post-ischemic inflammation following a stroke, which was absent in CCR2-KO mice (Garcia-Bonilla et al. 2018). Similarly, administration of *in vitro* IL-4- and IL-13-primed monocyte before the induction of stroke, ameliorates stroke-induced motor and cognitive dysfunction, which was independent of the infarct size (Ge et al. 2017).

5.5.1 The Microbiota in Stroke

The composition of the gut microbiota changes in response to severe stroke (Singh et al. 2016, Stanley et al. 2016, Stanley et al. 2018, Xia et al. 2019). The role of the microbiota in stroke outcome is highlighted by the findings that GF mice, and mice that were administered additional antibiotics, show a reduced infarct volume in response to stroke (Benakis et al. 2016, Singh et al. 2018). Even though antibiotic treatment has also been reported to worsen stroke outcome in mice (Winek et al. 2016). Not surprisingly, transplantation of the microbiota from mice previously undergone stroke to GF mice results in larger infarct volumes in response to a subsequent stroke (Singh et al. 2016). Whereas the

transfer of a healthy mouse microbiota to mice one-day post-stroke reduces infarct volumes (Singh et al. 2016). Similarly, transplantation of the gut microbiota from acute ischemic stroke patients with a relatively more altered microbiota into mice results in a worse stroke outcome, compared to mice receiving the microbiota from stroke patients with relatively less stroke-induced alterations in gut microbiota composition (Xia et al. 2019). These data indicate a causal role for the microbiota in stroke responsiveness.

5.6 Multiple Sclerosis

Enhanced monocyte trafficking into the CNS has been observed in various conditions of neurodegeneration (Baufeld et al. 2018), such as human multiple sclerosis (MS) (Fischer et al. 2019), and its associated animal model experimental autoimmune encephalomyelitis (EAE) (Fife et al. 2000, Izikson et al. 2000, Mildner et al. 2009, Ajami et al. 2011, Jordao et al. 2019). MS is an autoimmune disease where the immune system attacks nerve cells leading to demyelination and disruption of nerve signalling. In EAE, CCR2+ monocytes migrate into the brain as early effector cells and facilitate the development of EAE (Mildner et al. 2009, Ajami et al. 2011), suggesting that monocytes may play a pivotal role during the early phases of MS-associated neuroinflammation and autoimmunity. Indeed, CCR2-KO mice show reduced inflammation and delayed disease onset (Fife et al. 2000, Izikson et al. 2000, Columba-Cabezas et al. 2002, Ajami et al. 2011). It is also interesting to note that monocytes from MS patients treated with type-I interferon, a common treatment for MS, secrete less IL-1β, a pro-inflammatory cytokine (Guarda et al. 2011).

5.6.1 The Microbiota in Multiple Sclerosis

The composition of the gut microbiota is altered in patients with MS (Chen et al. 2016, Berer et al. 2017, Cekanaviciute et al. 2017, Zeng et al. 2019) and mice with EAE (He et al. 2019). A causal role for the microbiota in MS pathophysiology is illustrated by transferring the microbiota from MS patients to mice, resulting in a fastened EAE progression (Berer et al. 2017, Cekanaviciute et al. 2017). It is also interesting to note that intermittent fasting confers protection to EAE through the gut microbiota

(Cignarella et al. 2018). Similarly, depletion of the microbiota using antibiotics in a mouse model of MS prevents motor dysfunction, limits axon damage and delays the onset of clinical score, while decreasing spatial memory (Mestre et al. 2019, Zeraati et al. 2019). These results indicate a promising prospect of alleviating MS symptomatology using microbiota-targeted strategies. Interestingly, MS patients supplemented with a probiotic containing *Lactobacillus*, *Bifidobacterium* and *Streptococcus* reduced the frequency of classical monocytes (Tankou et al. 2018). Similarly, supplementation with *L. acidophilus, L. casei, B. bifidum*, and *L. fermentum* improves expanded disability status scale scoring, and depression and anxiety measures (Kouchaki et al. 2017). In addition, *L. reuteri* administration reduces the development of EAE in mice (He et al. 2019).

5.7 Alzheimer's Disease

Alzheimer's disease (AD) is associated with an enhanced myeloid cell trafficking into the brain, compared to normal ageing (Martin et al. 2017). AD is a neurodegenerative disease associated with neuroinflammation, neuronal cell death, an accumulation of amyloid-β in the brain and progressive dementia. Monocytes derived from AD mouse models and late-stage patients with AD show an inflammatory phenotype (Saresella et al. 2014, Martin et al. 2017, Thome et al. 2018). These monocytes seem to be involved in the clearance of amyloid-β (Michaud et al. 2013, Martin et al. 2017, Guo et al. 2019), indicating that these cells can reduce AD pathophysiology. In fact, bone marrow-derived macrophages are more efficacious in amyloid-β phagocytosis and clearance than brain microglia (Simard et al. 2006). The protective role of monocytes in AD is further illustrated by the fact that CCR2-KO accelerates amyloid-β accumulation in the hippocampus and prefrontal cortex and expedites cognitive decline in mouse models of AD (El Khoury et al. 2007, Mildner et al. 2011, Naert et al. 2011, Naert et al. 2012). It is also interesting to note that elevated plasma CCL2 levels have been reported in individuals with early-stage AD, even though CCR2 receptor levels on monocytes were decreased (Zhang et al. 2013).

5.7.1 The Microbiota in Alzheimer's Disease

The composition of the gut microbiota is altered in patients with AD (Unger et al. 2016, Vogt et al. 2017, Zhuang et al. 2018), as well as in rodent models (Harach et al. 2017, Sun et al. 2019). Interestingly, a GF mouse model of AD shows a reduced amyloid-β accumulation (Harach et al. 2017). And similarly, depletion of the gut microbiota using an antibiotic cocktail reduces amyloid-β deposition yet increases soluble Aβ levels (Minter et al. 2016). Targeting the gut microbiota in a mouse model of AD using a probiotic formulation containing *S. thermophiles, B. longum, B. breve, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. delbrueckii subsp. bulgaricus, L. brevis* reduces amyloid-β deposition, brain damage and cognitive decline (Bonfili et al. 2017, Bonfili et al. 2018). Similarly, supplementing a probiotic containing *L. acidophilus, L. casei, B. bifidum,* and *L. fermentum* improves cognition to AD patients improves cognition (Akbari et al. 2016).

5.8 Parkinson's Disease

Parkinson's disease (PD) is the most common neurodegenerative movement disorder and is characterised by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta along with the presence of Lewy bodies and Lewy neurites composed of α-synuclein throughout the CNS (Harms et al. 2018). PD is also associated with increased infiltration of monocytes into the brain (Harms et al. 2018). Interestingly, CCR2-KO mice show attenuated α-synuclein-induced neuroinflammation and degeneration of dopaminergic neurons (Harms et al. 2018). Functionally, monocytes from patients with PD show enhanced phagocytoses and reduced glucocerebrosidase activity, of which the latter is often associated with PD symptomatology (Atashrazm et al. 2018, Wijeyekoon et al. 2018).

5.8.1 The Microbiota in Parkinson's Disease

Alterations in the composition of the gastrointestinal microbiota have been observed in both PD patients (Hasegawa et al. 2015, Keshavarzian et al. 2015, Scheperjans et al. 2015, Aho et al. 2019, Barichella et al. 2019), and animal models (Sampson et al. 2016). Transferring the microbiota from PD

patients to a GF mouse model of PD results in α-synuclein-mediated motor deficits (Sampson et al. 2016). Furthermore, the GF mouse model of PD shows ameliorated motor and gastrointestinal dysfunction, microglia inflammation and α-synuclein pathology, compared to their conventional PD counterparts (Sampson et al. 2016). Subsequent SCFA supplementation to these GF mice promotes α-synuclein-mediated neuroinflammation (Sampson et al. 2016). Whereas individuals who have undergone a vagotomy, disrupting one of the major pathways in microbiota-gut-brain communication, have reduced risk of developing PD (Svensson et al. 2015, Liu et al. 2017). Importantly, it was recently even shown that propagation of α-synuclein from the gut to the brain via the vagus nerve causes PD in mice (Kim et al. 2019). Overall, these results show a causal role for the gut microbiota in PD pathology. Finally, it is interesting to note that gut microbial tyrosine decarboxylases decrease levels of levodopa in the treatment of PD (van Kessel et al. 2019).

6. Conclusion

It is crucial that we appreciate the complex role of monocyte trafficking in regulating brain function and its behavioural consequences in order to understand their role in brain health and disease. Deficiencies in monocyte trafficking in absence of sickness or injury results in impaired adult hippocampal neurogenesis and memory retention (Mohle et al. 2016), whereas excessive monocyte trafficking is associated with negative consequences in conditions such as viral encephalitis (Getts et al. 2008, Kaufer et al. 2018), TBI (Hsieh et al. 2014, Israelsson et al. 2014), chronic stress (Wohleb et al. 2013, Mackos et al. 2016), EAE (Fife et al. 2000, Izikson et al. 2000, Columba-Cabezas et al. 2002, Ajami et al. 2011) and PD (Harms et al. 2018). Conversely, these infiltrating monocytes also contribute to the recovery from stroke (Wattananit et al. 2016) and mitigate the development of AD (El Khoury et al. 2007, Mildner et al. 2011, Naert et al. 2011, Naert et al. 2012). Thus, whether monocyte infiltration into the brain is beneficial or harmful is condition-dependent, and modulating monocyte trafficking and their properties should therefore be tailored to each disease condition. The gut microbiota could play a pivotal role here (**Figure 3**), as many versatile and distinct microbiota-targeted

strategies have already been developed (**Table 2**). Even though many of these microbiota-targeted strategies have not been investigated in light of monocyte trafficking, some research already shows possible implications.

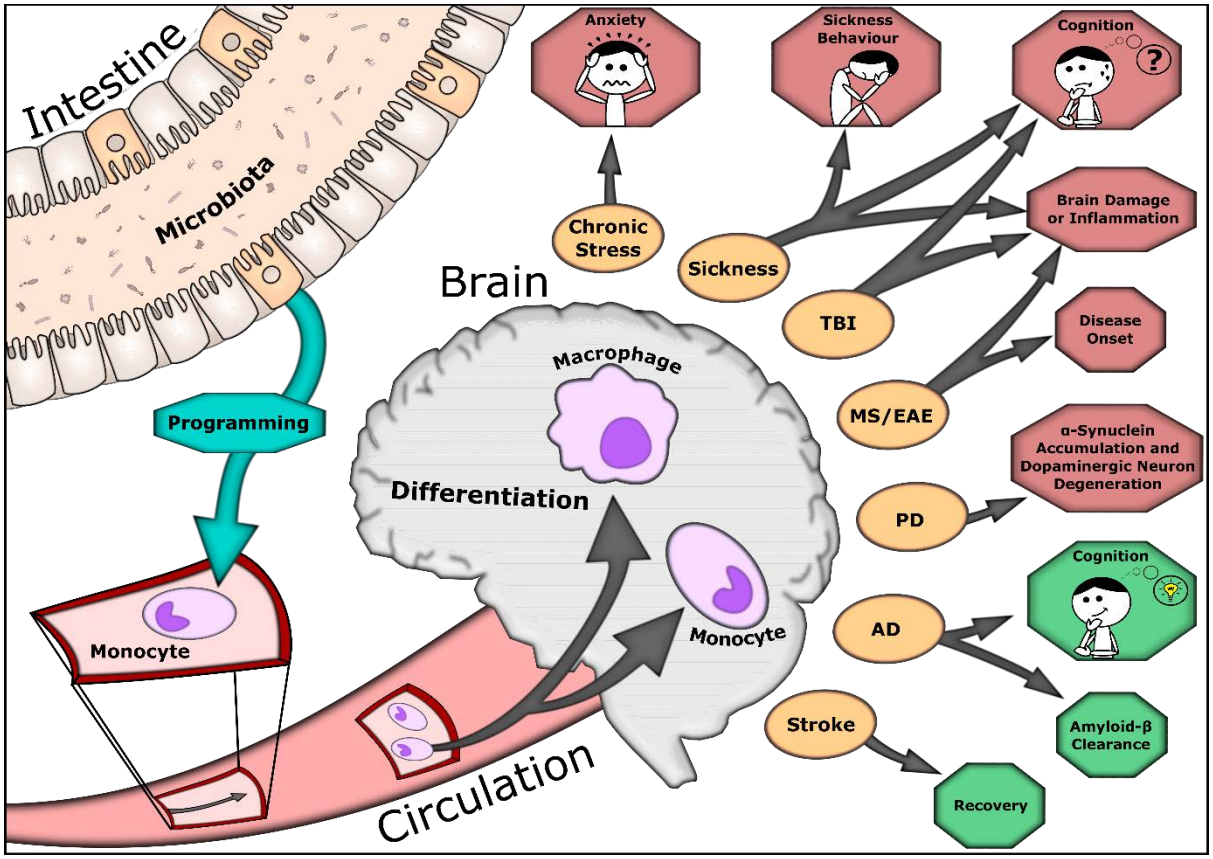

***Figure 3**: The therapeutic potential of microbiota-targeted strategies in conditions associated with increased monocyte trafficking into the brain. The microbiota can (epigenetically) program circulating monocytes, prior to their trafficking into the brain and subsequent differentiation into macrophages. These monocytes and monocyte-derived macrophages play a causal role in specific aspects of pathophysiology of various disease conditions, such as traumatic brain injury (TBI), experimental autoimmune encephalomyelitis (EAE) and human multiple sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD) and stroke, as well as conditions associated with chronic stress and sickness. Monocytes play a negative role (red boxes) or positive role (green boxes) depending on the disease condition.*

We have shown that a prebiotic-enriched diet ameliorated both monocyte trafficking into the brain and microglia activation in middle-aged mice (Boehme et al. 2019), which is similar to another study demonstrating that a high fibre diet containing inulin reduces the gene expression of inflammatory markers in the microglia of aged mice (Matt et al. 2018). Conversely, antibiotic administration decreases brain LY6C^{hi} monocyte levels in healthy mice, resulting in deficits in neurogenesis and memory retention, which was subsequently restored upon supplementation with the probiotic VSL#3 (Möhle et al. 2016). And similarly, VSL#3 has also been shown to attenuate the development of sickness behaviour, reduce microglia activation and decrease monocyte infiltration into the brain following bile duct ligation in mice (D'Mello et al. 2015). However, more research is needed to further illuminate microbiome-host interactions in the context of monocytes trafficking to the CNS and their implications in brain health and function, even though initial data shows great promise.

However, there are still many gaps in our understanding of how we can target monocyte trafficking to ameliorate disease symptomatology. Even though we know whether monocytes play a positive or negative role in many of these disease conditions, more information is needed as to how monocytes locally exert their effects in the brain. Novel techniques such as metabolomics and single-cell sequencing will likely play a pivotal role in the dissection of the role of monocytes in impacting the brain microenvironment. Recent studies suggest a therapeutic role for monocytes in AD, as they seem to be involved in the clearance of amyloid-β (Michaud et al. 2013, Martin et al. 2017, Guo et al. 2019). Knowing this allows us to screen for microbiota-targeted therapeutics, such as bacterial strains and metabolites, that enhance the ability of monocytes to clear amyloid-β. Particular in light of the ageing society, microbiota-based strategies that modulate monocyte behaviour could have a tremendous impact on novel therapeutics and the healthcare industry. However, we also need a better understanding of how and whether specific microbiota-derived metabolites can impact monocytes in the circulation prior to attachment to the endothelial vasculature and diapedesis and how this affects the macrophages they differentiate into. This would provide us with a better understanding of how we can modulate monocyte trafficking using microbiota-targeted strategies. Nonetheless, many

advances have been made over the last few years, which provides a promising prospect for microbiota-targeted strategies in altering monocytes and their functionality. Overall, this review provides an exciting starting point for the development of such therapeutics in improving brain physiology and behaviour in both health and disease.

Table 2. A summary of microbiota-targeted strategies studies for placebo-controlled human studies and animal studies.

Species/Model and Sex	Gut Microbiota-Targeted Strategy	Treatment Time and Dosage	Outcome	References
Multiple sclerosis (M/F)	*Lactobacillus acidophilus, L. casei, Bifidobacterium bifidum,* and *L. fermentum*	2 × 10^9 CFU daily for 12 weeks	Decreased depression and anxiety measures	(Kouchaki et al. 2017)
Individuals (M/F) affected by daily stress during the last month	Probio-Stick: *L. acidophilus Rosell-52* and *B. longum Rosell-175*	3 × 10^9 CFU per day for 3 weeks	Decrease in specific stress-induced gastrointestinal symptoms	(Diop et al. 2008)
Student (M/F) exam stress	Milk fermented with *L. casei Shirota YIT 9029*	1 × 10^9 CFU per day for 8 weeks	Ameliorated cortisol 1 day prior to the exam.	(Takada et al. 2016)
Student (M/F) exam stress	*L. plantarum 299v*	1 × 10^{10} CFU per day for 2 weeks	Decreased cortisol	(Andersson et al. 2016)
Brain injury (M/F)	30 g glutamine and 240 ml fermented milk with *L. johnsonii*	Enteral administration for 6-14 days	Shortened stay in the intensive care unit	(Falcão de Arruda et al. 2004)
Traumatic brain injury (M/F)	B. longum, L. bulgaricus, and Streptococcus thermophilus.	Enteral administration 1 × 10^9 CFU split over 7 dosages daily for 21 days	Shortened stay in the intensive care unit	(Tan et al. 2011)
Aged adults (M/F) (50-70 years)	Lactononadecapeptide with *L. helveticus CM4*	2.4 g Lactononadecapeptide with *L. helveticus* fermented milk per day for 8 weeks	Improved cognition	(Ohsawa et al. 2018)
Aged adults (M/F) (>65 years)	L. reuteri *DSM 17938*	1 × 10^8 CFU twice daily for 12 weeks	No significant effect on depression, anxiety or perceived stress	(Östlund-Lagerström et al. 2016)
Aged adults (M/F) (60-75 years)	*L. helveticus IDCC3801*	Four tablets daily for 12 weeks	Improved cognition	(Chung et al. 2014)
Alzheimer's disease (M/F)	*L. acidophilus, L. casei, B. bifidum,* and *L. fermentum*	2 × 10^9 CFU daily for 12 weeks	Improved cognition	(Akbari et al. 2016)
C57Bl/6 mice (M), LPS-induced sickness-behaviour	B-GOS®: 48% w/w GOS, 26% lactose, 14% glucose and 12% galactose	For 3 weeks in drinking water	Ameliorated anxiety-like behaviour	(Savignac et al. 2016)

C57Bl/6 mice (M), Traumatic brain injury	*L. acidophilus*	1 × 10^{10} CFU daily by oral gavage for 1 week starting 4 hours post operation	Decreased neurological severity score, neurodegeneration and lesion volume	(Ma et al. 2019)
C57Bl/6 mice (M), Traumatic brain injury	*Clostridium butyricum*	1 × 10^{9} CFU daily by oral gavage for 2 weeks before traumatic brain injury and for 2 weeks afterwards	Ameliorated neurological severity score, brain oedema and neurodegeneration	(Li et al. 2018)
F344 rats (M), Stress	*L. casei Shirota YIT 9029*	In food for 2 weeks	Ameliorated acute stress-induced cortisol	(Takada et al. 2016)
F344 rats (M), Stress	GOS, or polydextrose alone, lactoferrin alone, or GOS, polydextrose and lactoferrin	GOS, 7 g/kg; polydextrose, 7 g/kg; lactoferrin, 2.6 g/kg in food for 4 weeks	Ameliorated stress-induced learned helplessness	(Mika et al. 2017)
C57Bl/6 mice (M), Chronic stress	FOS and GOS	0.3-0.4 g/mouse per day in drinking water for 6 weeks	Ameliorated cognitive dysfunction, anhedonia, anxiety-like and depressive-like behaviour	(Burokas et al. 2017)
C57Bl/6 mice (M), Chronic stress	3'Sialyllactose or 6'Sialyllactose	In food (5%) for 2 weeks and during stress (1 week)	Ameliorated anxiety-like behaviour	(Tarr et al. 2015)
C57Bl/6 mice (M), Chronic stress	*L. reuteri*	2 × 10^{9} CFU in food for 4 weeks	Ameliorated despair behaviour	(Marin et al. 2017)
C57Bl/6 mice (M), Chronic stress	*L. rhamnosus JB-1*	1.67 × 10^{9} CFU per dose by oral gavage. 20 dosages over 28 days	Ameliorated social and anxiety-like behaviour	(Bharwani et al. 2017)
C57Bl/6 mice (M), Chronic stress	*L. helveticus MCC1848*	±1 × 10^{9} CFU in food for 2 weeks	Ameliorated anhedonia	(Maehata et al. 2019)
Sprague–Dawley rats (M), Chronic stress	*L. helveticus NS8*	1 × 10^{9} CFU/mL in drinking water for 3 weeks	Ameliorated corticosterone levels, anhedonia and anxiety-like behaviour	(Liang et al. 2015)
Swiss albino LACA mice (M), Chronic stress	*L. plantarum MTCC 9510*	2 × 10^{10} CFU daily by oral gavage for 4 weeks	Ameliorated cognitive impairments, anxiety- and depressive-like behaviour	(Dhaliwal et al. 2018)

Kunming mice (M), Chronic stress	*L. kefiranofaciens ZW3*	1 × 10^8 CFU daily by oral gavage for 6 weeks	Ameliorated depressive-like behaviour	(Sun et al. 2019)
C57Bl/6 mice (M), Chronic stress	Short-chain fatty acids	Sodium acetate (67.5mM), sodium propionate (25mM), and sodium butyrate (40mM) in drinking water for 11 weeks	Ameliorated anhedonia and stress-responsiveness	(van de Wouw et al. 2018)
Sprague–Dawley rats (M), Chronic stress	Short-chain fatty acids	Sodium propionate (200 mmol/L) 1 mL intrarectally daily for 5 weeks.	Ameliorated depressive-like behaviour	(Li et al. 2018)
Fischer 344 Rats (M), aged (18 months)	*L. plantarum KY1032* and *L. curvatus HY7601*	1 × 10^{10} CFU by oral gavage for 8 weeks	Ameliorated memory impairment	(Jeong et al. 2015)
C57Bl/6 mice (M), middle-aged (10 months)	FOS-inulin	In food (9.2% inulin, 0.8% FOS) for 3.5 or 14 weeks	Ameliorated infiltration of LY6C^{hi} monocytes into the brain and reduced microglia activation	(Boehme et al. 2019)
Balb/c mice (M), aged (22-25 months)	Inulin	In food (5%) for 4 weeks	Ameliorated expression of genes associated with inflammation in microglia	(Matt et al. 2018).
C57Bl/6 mice injected with myelin oligodendrocyte glycoprotein peptide and pertussis toxin (F), Experimental autoimmune encephalomyelitis	*L. reuteri*	1 × 10^{10} CFU by oral gavage for 20 days	Reduced clinical score	(He et al. 2019)
C57Bl/6 mice injected with myelin oligodendrocyte glycoprotein peptide (F), Experimental autoimmune encephalomyelitis	Antibiotic cocktail	neomycin (10 mg/ml), ampicillin (1 mg/ml), metronidazole (10 mg/ml), vancomycin (5 mg/ml) and Amphotericin-B (0.1 mg/ml) via drinking water for 12 weeks	Reduced onset of clinical score and decreased spatial memory	(Zeraati et al. 2019)

TMEV-IDD SJL/J mice (F), Experimental autoimmune encephalomyelitis	Antibiotic cocktail	ampicillin (1 mg/mL), metronidazole (1 mg/mL), neomycin sulfate (1 mg/mL) and vancomycin (0.5 mg/mL) in drinking water for 2 weeks	Reduced motor dysfunction and axon damage	(Mestre et al. 2019)
APPSWE/PS1ΔE9 mice (M), Alzheimer's disease	Antibiotic cocktail	Gentamicin (0.02 mg/ml), vancomycin (0.01 mg/ml), metronidazole (0.04 mg/ml), neomycin (0.01 mg/ml), ampicillin (0.02 mg/ml), kanamycin (0.06 mg/ml), colistin (120 U/ml) and cefaperazone (0.02 mg/ml) in drinking water until 6 months of age	Reduced Aβ deposition, but increased soluble Aβ levels	(Minter et al. 2016)
3xTg-AD mice (M), Alzheimer's disease	SLAB51: *S. thermophiles, B. longum, B. breve, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. delbrueckii subsp. bulgaricus, L. brevis*	2×10^{11} CFU /kg in drinking water bodyweight per day	Reduced cognitive decline, brain damage, and Aβ deposition	(Bonfili et al. 2017, Bonfili et al. 2018)
Thy1-α-synuclein mice (M), Parkinson's Disease	Antibiotic cocktail	Ampicillin (1 g/L), vancomycin (0.5 g/L), neomycin (0.5 g/L), gentamycin (100 mg/L), and erythromycin (10 mg/L) in drinking water for 7 weeks	Ameliorated motor function	(Sampson et al. 2016)
Thy1-α-synuclein mice (M), Parkinson's Disease	Short-chain fatty acids	Sodium acetate (67.5mM), sodium propionate (25mM), and sodium butyrate (40mM) in drinking water for 7 weeks	Increased microglia activation and motor dysfunction	(Sampson et al. 2016)

Abbreviations: M, males; F, females; CFU, colony-forming units; LPS, lipopolysaccharide; GOS, galacto-oligosaccharide; GOS, fructo-oligosaccharide; Aβ, amyloid beta.

Competing interests

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